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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/416,812	10/13/99	RAMACHANDRA M	CJ-0926KUS

HM22/0730

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EXAMINER	
SORRELL O, E	
ART UNIT	**PAPER NUMBER**
1633	11

DATE MAILED: 07/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/416,812	Applicant(s) RAMACHANDRA ET AL.	
	Examiner Eleanor Sorbello	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to amendment

1. Applicant's amendment and response to the official Office Action mailed November 11, 2000 has been received and filed on May 29, 2001 as Paper No. 10. **Claims 1-40 are pending.** Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's argument.

Claim Objections

2. Claim 3 is objected to because it recites the phrase "genus adenoviridiae". The term Adenoviridae was misspelled. Further, Adenoviridae is a family and not a genus.

3. Applicant's arguments are addressed below on a per section basis. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Claims 1-40 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record as set forth in the official action of November 11, 2000, because the specification, while being enabling for the construction of a selectively replicating adenoviral vector comprising a TGF-β pathway responsive promoters (such as PAI-1 promoter and SRE-promoter) and p53 pathway responsive promoters (such as p53CON and RGC) operably linked to a repressor of viral replication, does not reasonably

provide enablement for the (1) construction of any viral vector comprising pathway responsive promoters operably linked to a repressor of viral replication or (2) pharmaceutical compositions comprising any viral vector and (3) methods of killing cells *in vivo* or *ex vivo* by contacting target or host cells with the aforementioned recombination viral constructs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, as argued earlier.

Applicants however, claim that any viral vector administered via any route comprising a promoter responsive to any pathway, is enabled, because numerous patents have issued, wherein administration of a viral vector is central to the invention. However as argued herein and in the previous two office actions, examiner understands from the state of the art that administration of a viral vector for a specific purpose is unpredictable and therefore, in vitro results cannot simply be extrapolated to that which might occur in vivo.

Applicant argues vehemently against the rejections of claims 1-40, under 35 U.S.C. 112, first paragraph set forth in office action mailed November 13, 2000, because applicant believes that they have set forth an enabling invention, and that the standard of review being applied to this application is improper.(See page 2 of Response received 5/21/01). Applicants do not feel that their claims are (i) overly broad and believe that one skilled in the art should be able to construct viral vectors based on the specification and (ii) in an invention that is in a field that is allegedly unpredictable but that one skilled in the art should be able to use the instant invention in *in vivo* methods, without undue experimentation. Examiner maintains however, that the claims

are directed to any recombinant viral vector which includes retroviruses, HSVs, AAVs and chimeric viral vectors etc. but the specification only teaches adenoviral vectors and plasmids. Additionally the broad claim is directed to any pathway responsive promoter, which may include promoters in the insulin pathway, thyroid pathway, cholesterol pathway and any other pathway. However, the specification only teaches promoters in the p53 pathway and TGF-beta pathway. Therefore examiner believes that applicants claims are unduly broad and are not commensurate with the guidance set forth in the specification. The claims are directed to all recombinant viruses. Robbins et al. teach viral vectors which are specific for certain applications and other viral vectors that were more appropriate for some other applications. In the instant invention, the vector used is required for cytolytic purposes. The only viral vector taught is the adenovirus. Retroviruses and AAVs are not known to be cytolytic. The specification lacks guidance as to the construction of retroviruses, HIVs and AAVs that are cytolytic. Therefore, because the prior art does not provide guidance for the construction of viral vectors for specified functions, the results obtained by the administration of viral vectors *in vivo* is unpredictable, and therefore full guidance in the specification is required as to how to make and use the viral vectors claimed. Applicants have only provided guidance for adenoviral vectors and plasmids, but the claims are directed to all viral vectors which are not commensurate in scope with the claims.

Applicants explain that their invention is drawn to the administration of vectors which selectively replicate in tumor cells that are defective in the p53 or Rb pathways (and therefore the tumor cells divide uncontrollably), and thereby cause the tumor cells to be killed due to the excess division of the viral vectors within the target cell.

Applicants also point out that the pathway responsive promoter is linked to a repressor of viral replication, thereby allowing viral replication in those cells that are defective in the p53 responsive promoter. Applicants claims are drawn to "any pathway responsive" promoter. Therefore applicants claims are unduly broad as the specification does not provide any guidance and applicants have not described all promoters that are responsive to all biochemical pathways. This would include both up regulation and down regulation of the pathway. For example, applicants have not provided guidance as to how one of skill in the art is to use a "steroid pathway responsive" promoter for instance, to kill cells, and it is not clear that one of skill in the art will know how to select the target cells for this experiment. Applicants have only taught p53 and TGF-β responsive promoters and their use in the context of killing tumor cells. In view of the lack of guidance in the specification, applicants claims are considered unduly broad and not commensurate in scope with the guidance in the specification.

Applicants refute the reference by Dang in that according to applicants, Dang commented only on funds that need to be used for gene applications. Applicants argue with examiner's interpretation of Dang's statements and dismisses examiner's interpretation that gene therapy is a "pipe dream". (See page 3, paragraph 3). Applicants interpretation of Dang's statements were that he analogized gene therapy to other therapies once considered fanciful. However, Dang underscored the unpredictability of current gene therapy methods, even though there are a few that are enabled, and stated the importance of using a number of animal models including immunocompetent animals to study delivery by viral vectors of Factor IX to

immunocompetent dogs as compared to the delivery of retroviral vectors to nude mice. (See page 471, paragraph 2).

Applicants argue that the lack of in vivo examples does not preclude a finding of patentability of the claimed subject matter. (See Response page 4, line 32). Applicant restates that the examiner is applying an improper standard to evaluate the instant invention by referring to it merely as "gene therapy". (See Response, page 5, line 11). As examiner has mentioned earlier, *in vitro* examples cannot be extrapolated to *in vivo* situations where the prior art does not teach one how to make and use any viral vector for specified outcomes, and the specification does not provide guidance for such.

Applicant refers to numerous patents that have issued in gene therapy to support applicant's view that gene therapy is enabled across the board. However examiner disagrees. It is clear that the contents of a patent application which may be available as "prior art" under § 102(e) to show that another was the first inventor may not have been known to anyone other than the inventor, his attorney, and the Patent Office examiner, and perhaps the assignee, if there was one, until it issued as a patent. As of its filing date it does not show what is known generally to "any person skilled in the art," to quote from § 112. On the other hand, § 112 requires an applicant to so describe his invention as to enable any person skilled in the art to practice it, the purpose being to make the invention understandable to all such persons as soon as the patent issues. Sections 112 and 102(e) rest on different foundations, serve different purposes, and are not comparable. There is nothing "unfair" about the situation. (*In re Glass,* 181 USPQ 31, 34 (CCPA 1974). The patents referred by applicant are summarized below and are not relevant to applicants disclosure and are not supported by applicants disclosure.

US Patent NO: 6,204,251, issued March 20, 2001, is drawn to ocular gene therapy where specific viral vectors are used for the delivery of the therapeutic gene. US. Patent No: 6174871, issued January 16, 2001, drawn to a method of treating heart disease by delivering a replication-deficient adenovirus vector to at least one left or one right artery, wherein a protein expressed by the gene expression causes the increase in contractile function of the myocardium. Specific teachings were present wherein a specified number of particles were delivered, the specific sites of delivery required for the instant invention were also taught. US. Patent No: 5871726, issued February 16, 1999, entitled tissue specific and tumor growth suppression by an adenovirus comprising PSA, and claim 1 is directed to an adenovirus comprising a promoter comprising an enhancer from a PSA gene, which included an in vivo method for such a use. Examiner contends that the applicants in this case are claiming tissue specific promoters in an adenoviral vector and showed construction of such and administration to art accepted models of the human diseased state. US. Patent No: 6197293 are directed specifically to adenoviral vectors to be used in a method of supressing tumor cell growth, by contacting the tumor cell wherein adenovirus enters the tumor cell and exhibits cytotoxicity for the tumor cell. In this case, the applicants show direct injection into a tumor cell with an adenoviral vector which is currently an enabled method for gene therapy. US Patent No: 6,066,624 is also directed to methods in which a direct injection of adenoviral vectors into tumors cause regression of the solid tumor. This method as explained above is enabled. US. Patent No: 6,096,718 is directed to tissue specific adenoviral vectors for breast cancer treatment in mammals by delivering a replication incompetent adenovirus with HSV-TK gene and subsequently administering

an effective dose of gancyclovir, whereby the breast cancer cells of the mammal are killed. US Patent No: 6,100,242 directed to a method of increasing contractile function by directly injecting into the coronary artery a transgene delivered via a replication-deficient adenoviral vector encoding an angiogenic protein. US 6,001,816 is directed to a method for the administration of an adenoviral vector administered intravenously comprising a DNA sequence encoding a leptin which causes decrease in body weight of the mammal. US 5,830,458 that is directed to a method for destroying a human cell that is infected with a virus or a canerous cell or a gvhd cell, by administering a replication defective recombinant retrovirus comprising a gene encoding a protein which converts a purine-based or pyrimidine based drug to another compound that is toxic to the cell. All the patents summarized above are gene therapy patents that have enabling disclosures, and have been issued after the filing date of the instant application. Because the prior art of record does not supplement the deficiencies in the specification, applicants are required to support claims by an enabling disclosure due to the unpredictability in delivering a gene and obtaining the desired response.

Contrary to applicants argument (See page 8, last paragraph), that these applications are not limited to certain diseased states, or particular modes of administration or certain vectors, in each of the above issued patents, the specific applicant taught specified gene therapy vectors, administered by specified routes of administration ie. intravenous or direct tumor injection, or the viral vectors comprised tissue specific promoters.

Applicants however, claim that any viral vector administered via any route comprising a promoter responsive to any pathway, is enabled, because numerous gene

therapy patents have issued. However as argued herein and in the previous two office actions, examiner has shown that the field of gene therapy is unpredictable and in vitro results cannot simply be extrapolated to that which might occur in vivo.

Claim Rejections - 35 USC § 102

5. Claim 35 stands rejected under 35 U.S.C. 102(e) as being anticipated by Buckbinder et al. (US. Pat. No: 5,886,149).

Applicant claims a p53 pathway-responsive promoter selected from the group consisting of p53CON and RGC.

Contrary to applicant's argument that Buckbinder does not teach p53 responsive promoters specifically, examiner directs applicant to col. 15 (lines 50-65) and 16 (lines 1-12) of the issued patent wherein Buckbinder teaches p53RGC promoter sequences transfected with a luciferase reporter construct.

6. Claim 36 stands rejected under 35 U.S.C. 102(e) as being anticipated by Grainger et al. (US. Pat. No: 6,117,911).

Applicant claims a TGF-β pathway responsive promoter selected from the group consisting of PAI and SRE.

Contrary to applicant's argument that Grainger et al. does not teach the PAI promoter, examiner reiterates that Grainger does teach that the 4G allele of the PAI responsive promoter is the important component of the TGF responsive promoter. (See col. 33, lines 23-35). The only requirement that is required for the prior art to anticipate

is the fact that PAI is a TGF- β pathway responsive promoter. Therefore, Grainger et al. teach the components required for a 102(e) rejection.

Conclusion

7. Claims 1-40 stand rejected for reasons of record.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number

for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER